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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,716	11/30/2000	David F. O'Brien	15907-0022	4843

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/728,716	O'BRIEN ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The request for the continued examination and amendment filed on 4-17-2003 are acknowledged.

Claims included in the prosecution are 1 and 4-36.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1 and 4-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by the introduced expression, "said lipid and co lipid form preexisting lipid domains wherein the co lipids are Clustered in discrete domains". This means that clustered lipid and the co lipid, clustered in a specific preexisting formation are used in the formation of liposomes. However, a careful review of the specification indicates that it is not the case. Clarification is requested. Similarly, the method claim 27 (step I) recites, "capable of forming preexisting lipid domains wherein the co lipids are clustered in discrete domains. Since this is a method claims, how this is accomplished should be recited fully in steps I and ii).

Claims 32 and 33 recite 'liposome'; claim is dependent on claim 10, which recites 'liposome delivery system', and therefore, there is no antecedent basis for

the term 'liposome'. Claim 33, which also recites 'liposome', is dependent from claim 32.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 4, 9-11, 16-17, 23, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamparski (Biochemistry, vol. 31., 1992) of record.

Lamparski discloses liposomes containing a phospholipid (phosphatidylethanolamine or phosphatidylcholine) and a polymerizable co lipid (sorbPC) (note the abstract, Materials and Methods and Discussion).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the use of ionizing radiation is not taught by Lamparski. This argument is not found to be persuasive since in a composition claim, the intended use has no patentable significance; furthermore, since the polymerizable co lipid used by Lamparski is the same as in instant invention, one would expect the co lipid to polymerize upon exposure to ionizing radiation. Applicant argues that Lamparski

does not teach or suggest that the lipid and co lipid may form preexisting lipid domains wherein the co lipids are clustered in discrete domains. Applicant's arguments pertaining to substantially below the room temperature and therefore Lamparski does not disclose preexisting discrete domains are found to be persuasive since applicant provides no experimental evidence in support. Furthermore, as pointed out in the earlier action, a careful examination of the specification appear to indicate that the lipids in both instant invention and in the prior art are dissolved in the organic solvent and formed into a film and then hydrated. Since the lipids are in a solution form, one would expect the distribution of the lipids to be the same in both instances. Applicant has provided no experimental data to show the distribution is different in instant invention from that of the prior art. Furthermore, instant claims are composition claims and since the distribution of the lipids (whether random or discrete domain) is temperature dependent according to applicant, the distribution of lipids in the prior art preparations would be as 'discrete domains' below the room temperature; instant claims do not recite any temperature requirements. The declaration of Dr. O'Brien has already been discussed by the examiner in the prior action. The rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4-5, 9-11,16-31-33 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski cited above in view of either Heldebrant (5,061,484) or Charych (6,180,135) in further combination with Hallahan (6,159,443).

The teachings of Lamparski have been discussed above. In essence, Lamparski teaches instant liposomes and the destabilizing effect of ultra-violet on the liposomal membrane. What are lacking in Lamparski are the teachings of the use of X-rays for polymerization of the lipids and destabilizing the liposome. Although Lamparski does not specifically teach a method of administration of a therapeutic agent of a diagnostic agent, based on the studies Lamparski suggests the applicability of the radiation induced destabilizing of the liposome and the regulation of the release of the biological agents (note page 693).

Heldebrant while disclosing the administration of liposomal compositions to tumor bearing mice teaches that liposomal lipids can be polymerized by either UV radiation or by X-rays (col. 5, lines 14-23 and Example 4).

Charych teaches that liposomal lipids can be polymerized by either UV radiation or by X-rays (col. 11, lines 41-64).

It would have been therefore, obvious to one of ordinary skill in the art to use the liposomes of Lamparski for the delivery of the diagnostic or therapeutic agents with a

reasonable expectation of success since Lamparski provides guidance as to how to prepare the liposomes and suggests their use. Lamparski teaches only the application of ultraviolet radiation as the source as the ionizing radiation. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to use any form of ionization as long as they polymerize the lipid.

Hallahan discloses X-ray guided drug delivery to treat various neoplasms. The method involves administering the therapeutic agent or diagnostic agent in a delivery vehicle (liposomes) and irradiating the tissue using X-rays. The liposomes also contain antibodies attached to them. According to Hallahan such a method improves the drug delivery to the desired tissues (note the abstract, col. 1, line 61 through col. 6, line 58, col. 7, line 65 through col. 9, line 18, col. 15, line 18 through col. 17, line 9, col. 20, lines 6-49, col. 23, lines 10-59, Examples and claims).

The use of X-rays as the ionizing radiation with the liposomes of Lamparski would have been obvious to one of ordinary skill in the art since X-rays are not only another form of ionizing radiation to polymerize the liposomal lipids as shown by Heldebrant or Charych, but also provide an improved method of delivery when combined with delivery vehicles such as liposomes as shown by Hallahan.

7. Claims 5-8, 12-15 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski cited above in view of either Heldebrant (5,061,484) or Charych (6,180,135) in further combination with Hallahan (6,159,443) as set forth above, further in view of Woodle (BB, 1992) of record.

The teachings of Lamparski, Heldebrant, Charych and Hallahan have been discussed above. What are lacking in Lamparski and other references are the teachings of the inclusion of PEG in the liposomal compositions.

Woodle discloses that the inclusion of hydrophilic polymers such as PEG in liposomes stabilizes the liposomes and also improves the circulation time of these sterically stabilized liposomes when administered (pages 180-185 and 194-195).

The inclusion of PEG in liposomes of Lamparski would have been obvious to one of ordinary skill in the art since such an inclusion stabilizes the liposomes and also improves their circulation time when administered.

Applicant's arguments have been fully considered, but are deemed to be moot in view of these rejections. Applicant's arguments with regard to Lamparski have been addressed above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK